Amendments to the Drawings

The drawings and specification have been amended to correct the deficiencies as suggested by the Examiner.

The Examiner stated that reference character 100 has been used to designate both a macromolecule preparation process and apparatus. This has been rectified by the amendment to the specification on page 6, line 15.

The Examiner has also stated that the reference numeral 752 has been used to designate both waste site and aseptic fluid apparatus. The reference numeral for the waste site has been amended to be 792, and has been changed in Figure 7A to reflect the same.

The Examiner further stated that the reference characters 910 and 914 have not been mentioned in the description. These have been removed from the drawings.

Transmitted herewith are replacement drawing sheets consisting of a total of 26 sheets, figures 1-23, for filing in the subject patent application.

Attachment: Replacement Sheets

REMARKS

Objections and 35 USC 112 Rejections

Objections within the specification have been corrected as suggested by the Examiner. Claims 23, 41, and 45 have been amended to correct the minor informalities as stated by the Examiner. Claims 3 and 5 have been amended to correct the insufficient antecedent basis for the limitation "the sample source."

Further Claim Amendments

All independent claims 1, 18, 19, 20, 21, 24, 38, 39, 40, 41, 44, and 45 and dependent claims 3-5, 7, 9, 11, 23, 27, and 29 have been amended to clarify the subject matter. Claim 6 has been cancelled as the limitation has been added to amended claim 1.

Summary

The Examiner has rejected all claims over Swerdlow et al. (US 5,935,522) either alone or in combination with other references.

Without limitation to the claims, a disclosed embodiment will be discussed. Applicant describes an apparatus for capillary electrophoresis that includes an inlet chamber, an outlet chamber, and a capillary electrophoresis column. One end of the column is fixed at the interior of the inlet chamber. The column has a length of at least about 20 centimeters. Also included is a sample liquid source adapted for automatic control. The liquid sample source supplies a liquid sample through an input valve into the inlet chamber so that the sample is in fluid communication with the end of the column. The inlet chamber is connected to a waste chamber with a waste valve. The waste valve is closed as the sample is transferred from the inlet chamber to the electrophoresis column. An automated buffer liquid source also supplies buffer to the inlet chamber by operating a buffer input valve, once the sample is either completely used or drained from inlet chamber. Further, an automated cleaning liquid source supplies cleaning fluid to the inlet chamber and the capillary electrophoresis column by operating a cleaning input valve. All of these valves are independently controlled by an automated controller to direct the respective fluids at least into the inlet chamber.

When applicant's sample is supplied to the inlet chamber from the liquid sample source, it remains static within the inlet chamber, until it is introduced to the end of the column by pressure (hydrodynamic loading) or by electro-kinetic injection. (See Applicant's Figure 13.) Because the waste valve is closed during the transferring of the sample from the inlet chamber to the column, one skilled in the art would understand that a portion of the unused sample remains within the inlet chamber to be injected into the column later on to be drained. Because the Applicant's sample remains static within the inlet chamber during sample injection; the system is not a continuous sample loading system.

Swerdlow describes an apparatus suited for subjecting biological samples to sample preparation tasks. The apparatus includes a capillary electrophoresis device comprising a capillary electrophoresis column with an inlet end and an outlet end, a means of injection, and a means of applying a high voltage to cause the continuous differential migration of species of interest through the capillary column. Swerdlow utilizes continuous flow techniques to deliver the sample to the capillary electrophoresis column. Swerdlow's capillary is only loaded by electro-kinetic injection. An electric field must be present to obtain loading of the capillary electrophoresis column (Swerdlow, Col. 10, lines 16-42). The portion of the sample which is not loaded into the capillary electrophoresis column 116 flows through the tee 112 and continues to a waste chamber 11 (Swerdlow, Col. 10, lines 1-5). Swerdlow, therefore, does not teach the sample being static at any time, but having a continuous flow.

Swerdlow's buffer is supplied to the capillary electrophoresis column through a positive buffer chamber 120. Filling is accomplished by application of pressure from the pressure source to the positive buffer chamber 120 via a pneumatic valve system. After the run, the capillary is ready to process a new sample (Swerdlow, Col. 12, lines 9-17). The sample is then loaded by electro-kinetic injection in a continuous flow without any interruption of the sample stream flow (Swerdlow, Col. 12, lines 25-30).

Swerdlow further describes a loop wash device for sterilization 126 (Swerdlow, Col. 12, lines 20-25). One skilled in the art would understand that the loop wash device only sterilizes the injection loop 103. (See Swerdlow, Figure 1) It does not sterilize the tee 112 or the electrophoresis column 116.

All independent claims have been have been amended to add the limitations of a sample liquid source adapted for automatic control, that supplies a liquid sample through a sample_input valve into the inlet chamber, the sample supplied to be in fluid communication with the end of the column, a waste chamber in communication with the inlet chamber, the waste chamber having a waste valve that is closed as the liquid sample is transferred to the column, a buffer liquid source adapted for automatic control, that supplies a buffered liquid through a buffer input valve into the inlet chamber, the buffer supplied to be in fluid communication with the end of the column, a cleaning liquid source adapted for automatic control, that supplies a cleaning fluid through a cleaning input valve through the inlet chamber and the capillary electrophoresis column, and an automated controller adapted to control the sample input valve, the buffer input valve, and the cleaning input valve to direct the sample, buffer, and cleaning fluid into the inlet chamber.

These limitations are in contrast to Swerdlow, who describes a continuous loading system, in which the sample does not sit static within the tee at any time. Further, one skilled in the art would understand that Swerdlow's sterilization loop is only capable of sterilizing the sample loop 103, not the inlet chamber or the capillary electrophoresis column. Also, if sterilization of the electrophoresis column was desired through the loop wash device, the sterilization fluid would have to go through gel filtration HPLC column 106, which would destroy the column 106. Therefore, Swerdlow does not teach a cleaning liquid source that supplies a cleaning fluid through the inlet chamber and the capillary electrophoresis system.

Also, the portion of the of the sample that is not loaded onto the capillary flows through the tee and into the waste chamber (Swerdlow, Col. 10, lines 1-7). In contrast to Applicant's amended claims, the waste chamber is not closed while the sample is transferred from the tee to the capillary. If that was the case, Swerdlow's system would be not a continuous loading system.

Based on these amendments, Swerdlow alone or in combination with any of the cited references does not teach all of the limitations of any amended independent claim. The independent claims, and all claims dependent on the same, are allowable for at least these reasons. The applicant therefore requests that the 102(b) and 103(a) rejections of all claims be withdrawn.

102(b) Rejections

Claims 1-9, 12-17, 19-20, 24-30, 33-34, 36-37, 39 and 44 have been rejected under 35 U.S.C. 102(b) as being anticipated by Swerdlow et al. (US 5,935,522). In order to reject a claim under 35 U.S.C. §102(b), the reference must teach each and every element of the claim. As stated by the Federal Circuit, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As stated, independent Claims 1, 19, 20, 24, 39, and 44 have been amended to add the limitations of a sample liquid source, adapted for automatic control, that supplies a liquid sample through a sample input valve into the inlet chamber, the sample supplied to be in fluid communication with the end of the column, a waste chamber in communication with the inlet chamber, the waste chamber having a waste valve that is closed as the liquid sample is transferred to the column, a buffer liquid source adapted for automatic control, that supplies a buffered liquid through a buffer input valve into the inlet chamber, the buffer supplied to be in fluid communication with the end of the column, a cleaning liquid source adapted for automatic control, that supplies a cleaning fluid through a cleaning input valve through the inlet chamber and the capillary electrophoresis column, and an automated controller adapted to control the sample input valve, the buffer input valve, and the cleaning input valve to direct the sample, buffer, and cleaning fluid into the inlet chamber.

These limitations are not taught by Swerdlow. These claims, along with any claims dependent on the same are allowable for at least these reasons. Some dependent claims, will however, be discussed.

Dependent claim 3 has also been rejected over Swerdlow. Amended claim 3 recites the liquid sample source pressurizing the inlet chamber to create a pulsed pressure differential across the length of the column. One skilled in the art would recognize that this is hydrodynamic loading of the electrophoresis column. Swerdlow only loads the electrophoresis column by an electro-kinetic loading. Swerdlow states that an electric field must be present to obtain loaded of the electrophoresis column. Swerdlow utilizes continuous flow techniques to deliver the sample to the capillary electrophoresis column. Swerdlow states that electro-kinetic injection avoids the

problems associated with hydrodynamic loading. Therefore, Swerdlow describes a continuous application of an electrical current to load the capillary (electro-kinetic loading); whereas Applicant's claim 3 recites applying a pulsed pressure differential (hydrodynamic loading). Swerdlow, thus, does not teach every element of dependent claim 3.

Rejected dependent claim 14 recites a degas unit that removes at least a portion of gas dissolved in the liquid. Applicant describes an additional degas unit that can be part of the system for automatically and actively removing dissolved gas. Swerdlow describes the reduced baseline noise of the sample as a result of reduced particulates and reduced bubbles. The reduced bubbles are a result of the direct loading of the sample into the electrophoresis column using the tee (Swerdlow, Col. 13, lines 22-35). Swerdlow does not describe an additional, automated and active degas unit as part of the system. Therefore, Swerdlow does not teach all of the limitations of claim 14.

Rejected independent claim 20 has been amended as previously stated. Further, the Examiner has identified Swerdlow's thermal cycling device as a lysis unit that is inherently capable of lysing cells in a liquid mixture comprising cells and a macromolecule as is recited in claim 20. Nothing in Swerdlow's description suggests that the thermal cycling device is a lysing unit. The thermal cycling device is preferably a thermal cycler adapted to hold the samples in capillary tubes and air is used to rapidly transfer heat to and from the sample (Swerdlow, Col. 7, lines 15-25). Therefore, Swerdlow does not teach a lysis unit as is recited in independent claim 20.

Further, claim 20 also recites a filter to separate components from the macromolcule, wherein the components comprise insoluble lysed cell components. Because Swerdlow does not describe a lysis unit or any means of lysing the sample, the components of the Swerdlow's sample would not contain lysed cell components as recited in claim 20 that the HPLC column would separate. Also, applicant recites an inlet chamber that receives a sample, wherein the sample comprises macromolecules separated from the insoluble lysed cell components. Because Swerdlow does not describe the sample being lysed, the tee cannot receive lysed call components. Therefore, Swerdlow does not teach all of the limitations of independent claim 20.

Dependent claim 25 recites pressurizing the inlet chamber to create a pressure differential across the length of the column. Swerdlow does not describe this step, as the sample in

Swerdlow is only electro-kinetically loaded, while dependent claim 25 describes hydrodynamic loading. Swerdlow's tee, therefore, is not pressured to created a pressure differential as is Applicant's inlet chamber. Dependent claim 25 is thus, not anticipated by Swerdlow.

Accordingly, Applicant submits that base Claims 1, 19, 20, 24, 39, and 44 as amended herein are not anticipated, because the references do not teach each and every aspect of the claimed invention. All claims dependent on these claims contain all the elements of these base Claims and are allowable for at least the same reasons. Applicants respectfully request that the Examiner reconsider and withdraw the §102(b) rejection of these claims and all claims dependent on the same.

103(a) Rejections

The Examiner has rejected claims 10-11, 21-22, 31-32, 35 and 41-42 under 35 U.S.C. 103(a) as being unpatentable over Swerdlow et al in view of Goodale et al. (US 5,356,525); claims 18, 20, 38, and 40 under 35 U.S.C. 103(a) as being unpatentable over Swerdlow et al. in view of Peterson et al. (US 6,391,541); claims 23 and 43 under 35 U.S.C. 103(a) as being unpatentable over Swerdlow et al in view of Goodale et al as applied to claim 22 and 42 respectively, above and in further view of Peterson; and claim 45 under 35 U.S.C. 103(a) as being unpatentable over Swerdlow et al in view Peterson et al., Chow et al. (US 6,537,99) and Goodale et al.

In order to reject a claim under 35 U.S.C. §103(a), the Office Action must first establish a *prima facie* case of obviousness. Establishing a *prima facie* case of obviousness requires that: (I) there must be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (ii) there must be a reasonable expectation of success; and (iii) the prior art reference must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As stated, independent claims 1,18, 19, 20, 21, 24, 38, 39, 40, 41, 44, and 45 have been amended to add the limitations of a sample liquid source adapted for automatic control, that supplies a liquid sample through a sample input valve into the inlet chamber, the sample supplied to be in fluid communication with the end of the column, a waste chamber in communication with the inlet chamber, the waste chamber having a waste valve that is closed as the liquid

sample is transferred to the column, a buffer liquid source adapted for automatic control, that supplies a buffered liquid through a buffer input valve into the inlet chamber, the buffer supplied to be in fluid communication with the end of the column, a cleaning liquid source adapted for automatic control, that supplies a cleaning fluid through a cleaning input valve through the inlet chamber and the capillary electrophoresis column; and, and an automated controller adapted to control the sample input valve, the buffer input valve, and the cleaning input valve to direct the sample, buffer, and cleaning fluid into the inlet chamber.

Swerdlow alone or in combinations with any of the cited references, does not teach, suggest, or motivate these limitations. Therefore, these claims or any claims dependent on the same are allowable over Swerdlow and any of the cited references for at least the same reasons. Some of the claims, however, will be addressed.

Cited reference Goodale describes sample handling system for use with a sample segment and a plurality of capillaries. The handling system further includes an attachment portion to removably receive and retail the sample segment and a manifold adapted to removably retain the sample segment and plurality of capillaries.

Dependent claim 10 that is dependent on independent claim 1, has been rejected. The Examiner has stated that Goodale teaches a fluid sensor, and though Swerdlow does not teach a fluid sensor, it would have been obvious to include a fluid sensor in each chamber as taught by Goodale. The fluid sensor disclosed in Goodale, does not however, sense the sample, but the buffer. The level sensing circuit provides an output to the controller indicating that the buffer is at the predetermined level within the wash cell and that the electrophoresis conduit is full (Goodale, Col. 16, lines 34-44). Goodale only discloses the sensing of buffer outside of the electrophoresis circuit. Applicant's fluid sensors are at the chambers and can detect the amount of sample within the inlet and outlet chambers. Therefore, it would not be obvious to combine Goodale and Swerdlow to place fluid sensors at the chambers. Thus dependent claim 10 is allowable for at least this reason.

Rejected dependent claim 11, dependent on independent claim 1, recites as part of the claim, a filter to separate at least a portion of insoluble components from the liquid sample. The Examiner points to Swerdlow's HPLC column 106 as a filter which does the same. Swerdlow does not disclose the separation of insoluble components. The HPLC column is a separation

means to separate all buffer salts and dNTPs from the sample (Swerdlow, Col. 9, lines 2-13). One skilled in the art would understand that buffer salts and dNTPs are not insoluble components, but soluble components. Therefore, Swerdlow does not teach or suggest a filter that separates insoluble components from the liquid sample. Claim 11 is allowable over Swerdlow for at least this reason. Further, Applicant's initial sample comes from a bioreactor. One skilled in the art understands that samples from a bioreactor contain a large amount of debris, that Applicant's filters can separate. An HPLC column, however, would not be capable of separating debris and its functionality would be compromised if it did the same.

Rejected dependent claims 30, 31, 32, 34, and 35 are dependent on amended independent claim 24. Dependent claims 30, 31, and 34 are therefore allowable for at least these reasons over Swerdlow and Goodale. Further, claim 31 recites sensing the fluid level in at least one chamber. As previously stated, Goodale discloses sensing the buffer level outside of the sampling system, not sensing of the sample at the chamber. Claim 34 recites separating insoluble components from the macromolecule with a filter. As stated, Swerdlow's HPLC column does not separate insoluble components, but soluble components.

Also, with regard to dependent claim 35, the Examiner states that Goodale teaches a method of degassing liquid sample and buffer. Goodale nowhere teaches degassing the sample, but only degassing the buffer. Swerdlow, as explained, does not disclose degassing of the sample, but discloses reduced bubbles as a result of his sampling system. Therefore, neither Swerdlow nor Goodale alone or in combination teach or suggest all of the limitations of dependent claims 31,34, or 35. These claims are thus, also allowable for the stated reasons.

With regard to rejected claim 38, Applicant's would like to address Examiner's assertion that Swerdlow's HPLC column is like Applicant's fine filter. The HPLC column is not a fine filter but a gel filtration system for separating dNTP's and buffer salts, both being soluble components. Further, Applicant's fine filter is capable of separating debris, which would compromise the functionality of the HPLC column. Applicant's fine filter can separate insoluble components, and is also capable of being cleaned with a cleaning fluid, while the HPLC column is not. The HPLC column, is therefore, not equivalent to applicant's fine filter.

Based on the claim amendments and arguments, the applicant requests that the 103(a) rejections of all relevant claims be withdrawn. Accordingly, Applicants submit that all of the

claims are patentable and respectfully request that the Examiner reconsider and withdraw the rejections.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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